Relationship of Leukemia Risk to Radiation Dose Following Cancer of the Uterine Corpus

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Background: **Radiotherapy has been linked infrequently to secondary leukemia despite extensive exposure of the active bone marrow to ionizing radiation. Few studies include substantial numbers of elderly patients.** ***Purpose:*** **We evaluated women with cancer of the uterine corpus, the majority of whom were treated at older ages, to gain additional information on cancer risk following partial-body radiotherapy and to examine differences in risk between external-beam therapy and brachytherapy.** ***Methods:*** **A cohort of 110000 women with invasive cancer of the uterine corpus who survived at least 1 year following their initial cancer was assembled from nine population-based cancer registries. Cancer diagnoses occurred from 1935 through 1985, and most patients were diagnosed during the 1960s and 1970s. Radiation doses were computed to 17 sections of the active bone marrow for 218 women who developed leukemia and for 775 matched control subjects.** ***Results:*** **Radiotherapy did not increase the risk of chronic lymphocytic leukemia (CLL) (relative risk [RR] = 0.90; 95% confidence interval [CI] = 0.4-1.9). However, for all leukemias except CLL, a significant risk was identified (RR = 1.92; 95% CI = 1.3-2.9). Overall, the pattern of risk in relation to dose was erratic and was most consistent with a constant increased risk across the entire dose range. The risk following continuous exposures from brachytherapy at comparatively low doses and low dose rates (RR = 1.80; 95% CI = 1.1-2.8; mean dose = 1.72 Gy) was similar to that after fractionated exposures at much higher doses and higher dose rates from external-beam treatment (RR = 2.29: 95% CI = 1.4-3.7; mean dose = 9.88 Gy), indicating a large difference in the estimated risk per unit dose. Risk did not vary by age at first exposure; increased risks were apparent for irradiated patients aged 65 years or older (RR = 1.77; 95% CI = 0.9-3.5).** ***Conclusion:*** **The leukemia risk associated with partial-body radiotherapy for uterine corpus cancer was small; about 14 excess leukemia cases were due to radiation per 10000 women followed for 10 years. Women aged 65 years or older had a radiation risk comparable with that found in younger women. The relationship of leukemia risk to radiation dose was found to be complex due to the competing processes of cell killing, transformation, and repair. At very high doses delivered at high rates, destruction of cells likely dominates, and the risk per unit dose is low. In the low dose range, where dose was protracted and delivered at relatively low dose rates, the leukemia risk appears lower than that projected from risk estimates derived from the instantaneous whole-body exposures of atomic bomb survivors. [J Natl Cancer Inst 86:1315-1324, 1994]**

Ionizing radiation is an established human leukemogen *(1)*. Notable increases in leukemia have been observed in atomic bomb survivors *(2)*, radiologists *(3)*, patients treated for malignant *(4,5)* and benign *(6-9)* diseases, and children exposed in utero to diagnostic x rays *(10)*. Radiogenic leukemia has the shortest minimal latency of all cancers, appearing within about 2 years of exposure. The exposure–response relationship appears complex and depends on total dose to bone marrow, percent bone marrow exposed, and dose rate (dose/duration of exposure). Risk is higher among those exposed at younger ages; however, the risk among elderly populations has not been well studied. Among atomic bomb survivors who received an instantaneous whole-body exposure, the dose–response pattern appears linear-quadratic under about 4 Gy; above 4 Gy, the risk appears to fall or taper off *(1)*.

Surprisingly, most studies of patients irradiated for cancer demonstrate either no or only a small leukemogenic effect. This small leukemogenic effect is most likely due to the substantial cell-killing effects from partial-body radiation exposures at such high levels. To provide additional information on leuke-

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See "Notes" section following "References."

mia risk following different methods of radiotherapy, we evaluated women with cancer of the uterine corpus, the majority of whom were treated at older ages. This population enabled a comprehensive evaluation of dose-dependent risk from two considerably different treatment modalities: 1) external-beam therapy, in which dose is delivered at a high rate in multiple fractions over a 4- to 6-week period: and 2) brachytherapy, in which the exposure is continuous at a low rate over a period of 2-3 days.

Subjects and Methods

Case and Control Selection

A cohort of 110000 women with invasive cancer of the uterine corpus (or uterus, not otherwise specified) who survived at least 1 year following their initial cancer was assembled from nine population-based cancer registries.[1] Cancer diagnoses occurred over a period of 50 years, from 1935 through 1985, and most patients were diagnosed during the 1960s and 1970s. Women were excluded if the uterine corpus cancer was not histologically confirmed or if another malignancy occurred prior to the uterine corpus cancer. Registry incidence and mortality files were searched to identify potential cases of Ieukemia that occurred at least 1 year after the uterine corpus cancer diagnosis.

All eligible leukemia cases were reviewed and reclassified according to the French–American–British (FAB) Nomenclature Committee using available peripheral blood reports, bone marrow aspirates, biopsy specimens, and hematologic reports. Included in the study were 218 case patients with leukemia: 120 case patients with acute nonlymphocytic leukemia (ANLL), eight case patients with acute lymphocytic leukemia (ALL), 32 case patients with chronic myelogenous leukemia (CML), one case patient with myelogenous leukemia not classified as acute or chronic, and 57 case patients with chronic lymphocytic leukemia (CLL). Three registry diagnoses of leukemia were not confirmed on hematologic review and were excIuded from the study.

Control subjects were randomly selected from patients previously diagnosed with cancer of the uterine corpus and individually matched to case patients based on registry, exact calendar year and age (±5 years) at uterine cancer diagnosis, race, and survival greater than or equal to the period between the uterine cancer diagnosis and the leukemia diagnosis. Four control subjects were chosen for each non-CLL case patient, and two control subjects were identified for each CLL case patient. Control subjects had to be free of a second cancer within the defined time interval at risk for their case patient. A total of 775 matched control subjects were selected.

Trained abstractors recorded demographic information and treatment details for all study subjects from hospital records, radiotherapy clinics, and tumor registries using a uniform abstract form. Photocopies of detailed radiotherapy records were used by a medical physicist (M. Stovall) to calculate the radiation doses for each individual.

Radiation Therapy

Radiotherapy was given primarily as an adjuvant procedure to surgery to eradicate subclinical disease in the vagina, pelvis, and regional lymph nodes. Patients typically received high-dose external-beam therapy to the pelvis, intracavitary implants (brachytherapy) using radioactive sources, or a combination of both therapies. Brachytherapy usually consisted of radium implants (73%), although other isotopes such as cesium 137 (19%), cobalt (3.5%), and radon seeds (2.2%) were used. Implants typically delivered a continuous dose to the vagina or body of the uterus over several days (mean, 2.9 days) for an average of 4700 milligram-hours, i.e., amount of radium x hours of exposure. This results in a dose rate to bone marrow of about 0.04 cGy/min.

External pelvic irradiation was given using orthovoltage machines (160-300 kVp) until the mid-1960s when higher energy machines (cobalt-60, linear accelerators [2-25 MV photons] or betatrons [22-33 MV photons]) became more commonplace. External irradiation was most often delivered in 2 Gy fractions daily, five times per week for 4-6 weeks (usually 20-30 fractions). The total exposure time per fraction was roughly 1-5 minutes, depending on the machine and fields used, which translates to a dose rate to the bone marrow of about 10-40 cGy/min. The usual field configurations were central (or right and left) anterior and posterior pelvic fields. Additional left and right lateral fields were used infrequently (10%). About 7% of external-beam treatments included anterior and posterior abdominal fields in addition to the usual pelvic fields; a lower dose per fraction (1.2 Gy) was used for these patients with total dose delivered in about 36 fractions over a 6-week period. The field size varied considerably; 50% of the women were treated with an approximate 15 x 15-cm field and another 20% with larger fields (17 x 17 cm to 25 x 20 cm).

Radiation doses were computed for 17 sections of the bone marrow. Dose estimates included any pelvic and abdominal radiation given as primary treatment for the uterine corpus cancer during the 1st year following diagnosis. Procedures for estimating radiation dose were based primarily on a mathematical model simulating a patient in which measurements in a water phantom were used. Dose estimates took account of field size, radiation energy, and field configurations and included contributions from primary beam, scattered radiation, and head leakage. The techniques used to estimate dose were similar to those used in past epidemiologic studies *(4,11).* A score from 1 to 5 was assigned to each patient to indicate whether the radiation dose record was complete and the seriousness of any missing information. Scoring was done without regard to case-control status.

Table 1 gives the mean active bone marrow dose for each bone marrow component for patients with known radiation dose. The mean weighted dose to the total active bone marrow was computed for each woman as the weighted sum of the dose (D_i) to each bone marrow component $(\Sigma\, w_i D_i)$, where w_i is the proportion of active bone marrow contained in the i th marrow component *(12).* Overall, the mean weighted dose estimate was 5.2 Gy for all modalities combined, 1.7 Gy for brachytherapy, and 9.7 Gy for external-beam therapy. There was little overlap between the dose distributions for the two radiation modalities; 90% of women treated with brachytherapy alone had mean doses in the range of 0.7-2.7 Gy versus 6.4-14.0 Gy for any external-beam therapy.

Statistical Analysis

Relative risk (RR) estimates (odds ratios) of radiation effects were calculated by comparing the odds of radiation exposure among the case patients with that of matched control subjects using conditional logistic regression methods *(13,14).* Two-sided, 5% statistical tests (corresponding to 95% confidence intervals [CIs]) were used. Variations in the effect of radiation on leukemia risk by age, calendar year, time since treatment, and registry (i.e., the matching factors) were evaluated using interaction variables in a multivariate model. Radiation given for other conditions or for cancer recurrence had no effect on leukemia risk; thus, no adjustment was made for other radiation in the analyses presented.

An initial assessment of the relationship between leukemia risk and radiation dose was made by classifying women into several categories based on their mean weighted marrow dose and by comparing each level to the referent group of patients not treated with radiotherapy. Dose groups similar to those used in an international cervical cancer study *(4)* are presented to facilitate comparison of results.

Using generalized risk models suggested from radiobiological theory and experimental studies, we evaluated the shape of the dose–response relationship *(1,15).* Guided by the approach used in the international cervical cancer study *(4),* we first tested a model hypothesizing a linear increase in risk with increasing dose (linear model: $RR = 1 + \alpha D$), where α is the coefficient to be estimated and D is the weighted mean dose to the active bone marrow for each individual. Next, models were fit that incorporated a linear induction term multiplied by an exponential "cell-killing" term that allowed the overall risk to decrease at high dose levels: linear-exponential $RR = (1 + \alpha D)(\exp \beta D)$, where α and β are the coefficients to be estimated. To account for the heterogeneous distribution of radiation dose to the active bone marrow, we also evaluated other models developed for the international cervical cancer study *(16)* that computed the overall RR as the weighted sum of the individual risks for each of the 17 bone marrow components: $RR(D_1,\ldots D_{17}) = \Sigma_i w_i (1 + \alpha D_i)(\exp \beta D_i)$. Here, D_i and w_i are the dose and the proportion of active bone marrow, respectively, for the i th bone marrow component. These models assume a homogeneous dose distribution within each marrow site; thus, in principle, derived risk estimates are comparable to those computed for populations experiencing uniform radiation exposure. Possible movement (or repopulation) of bone marrow stem cells from one site to another, dose rate, or fractionation are not considered in these models. Comparison between two nested models was evaluated statistically by computing the difference between the two model deviances, which is distributed as a chi-square statistic with degrees of freedom equal to the difference in number of parameters being estimated in the two models.

Table 1. Mean dose to bone marrow site among women treated with radiotherapy for uterine corpus cancer

Bone marrow site	Mean dose, Gy*			% of total ABM mass†	Weighted mean dose, Gy‡
	Brachytherapy only	External beam only	All radiation		
Cranium	0.01	0.04	0.03	7.6	0.002
Mandible	0.01	0.06	0.04	0.8	<0.001
Cervical spine	0.01	0.06	0.04	3.9	0.002
Clavicle	0.03	0.11	0.06	0.8	<0.001
Scapula	0.07	0.15	0.12	2.8	0.003
Sternum	0.18	0.41	0.28	3.1	0.009
Thoracic spine	0.18	0.76	0.42	16.1	0.068
Ribs (upper)	0.11	0.20	0.16	5.4	0.009
Ribs (middle)	0.18	0.80	0.43	5.4	0.023
Ribs (lower)	0.46	1.83	1.02	5.4	0.055
Lumbar vertebrae (1-2)	0.58	3.69	1.88	4.9	0.092
Lumbar vertebrae (2-3)	1.46	7.57	4.27	4.9	0.209
Lumbar vertebrae (5)	3.44	32.31	15.46	2.5	0.386
Sacrum	5.06	42.82	20.66	9.9	2.045
Pelvic bones	5.06	18.34	11.41	17.5	1.997
Upper femur	1.56	8.00	4.66	6.7	0.313
Humeri	0.05	0.07	0.06	2.3	0.001
Total ABM‡	1.72	9.67	5.21	100.00	5.215

*Mean dose was based on 576 patients with complete dose information (10 cases and 33 controls with unknown dose were excluded).
†Percent of active bone marrow (ABM) was taken from Cristy *(12)*.
‡Weighted mean dose for each bone marrow site is mean dose x (% active marrow/100). Weighted mean for total active bone marrow is sum of weighted mean for each bone marrow site.

Results

Most patients with uterine corpus cancer were older than 60 years at initial diagnosis (mean age, 62 years) and were treated during the 1960s and 1970s (mean year, 1970). Cancer was localized to the endometrium at initial diagnosis in 83% of women (case patients, 81%; control subjects, 84%). Three fourths of all leukemias occurred within 10 years after first treatment (mean, 7 years; range, 1-28 years).

Although surgery (hysterectomy and oophorectomy) was the mainstay of therapy for practically all study subjects (Table 2), radiotherapy had a major treatment role and was administered to about two thirds of women enrolled in this study. A little over one half of irradiated women were treated with brachytherapy

Table 2. Treatment and quality of radiotherapy information for case patients with leukemia following uterine corpus cancer (UCC) and their matched control subjects

Parameter	Leukemia cases, %			All controls, % (n = 775)
	Non-CLL (n = 161)	CLL (n = 57)	Total (n = 218)	
Treatment				
Surgery	88.2	89.5	88.5	91.0
Primary radiotherapy for UCC	73.3	63.2	70.6	60.0
Type of radiotherapy*,†				
Brachytherapy alone	49.2	61.1	51.9	55.9
External beam alone	20.3	19.4	20.1	21.7
Both external beam and brachytherapy	29.7	19.4	27.3	20.7
Unknown type	0.8	0.0	0.7	1.7
Type of external beam†,‡				
Orthovoltage	18.4	35.7	21.9	18.8
Cobalt-60	32.2	28.6	31.5	37.1
Betatrons	8.5	7.1	8.2	8.1
Other megavoltage§	30.5	21.4	28.9	30.5
Unknown type	10.2	7.1	9.6	5.6
Radiotherapy for other conditions	7.5	8.8	7.8	5.3
Alkylating agent therapy	5.0	3.5	4.6	2.2
Hormonal therapy	8.1	3.5	6.9	8.8
Quality of radiotherapy dose information*,†				
Very good	49.1	41.7	47.4	45.2
Good	37.3	41.7	38.3	39.1
Fair	5.9	13.9	7.8	8.6
Incomplete information	7.6	2.8	6.5	7.1

*Percent of all patients given radiotherapy (non-CLL case patients, n = 118; CLL case patients, n = 36; control subjects, n = 465).
†Percents do not always add to 100% because of rounding.
‡Percents given in table are percents of all patients receiving external-beam therapy (non-CLL case patients, n = 59; CLL case patients, n = 14; control subjects, n = 197).
§Other megavoltage machines are primarily linear accelerators.

alone, and about 20% each had external-beam therapy alone or external irradiation combined with brachytherapy. For three case patients and 19 control subjects, it was unknown if radiotherapy was given; because of the matched case–control design, four case patients and 26 control subjects were excluded from all analyses. Radiation doses could be estimated for 93% of irradiated patients; the quality of these records was rated as very good (complete record) or good (mostly complete with minor problems) for about 85% of irradiated patients.

Risk by Leukemia Subtype and Radiation Modality

Women treated with a weighted mean dose of 5.2 Gy from radiotherapy had a small but significantly increased risk of leukemia (RR = 1.64) (Table 3). Alkylating agents were significantly linked to leukemia risk (RR = 2.25; 95% CI = 1.0-5.1); when appropriate, analyses were controlled for this confounding exposure. No increase in risk was seen for CLL (RR = 0.90), a malignant condition rarely linked to ionizing radiation, or for ALL (RR = 0.73), although only eight ALL cases were observed. The strongest association with radiation was seen for the ANLL subtypes (RR = 2.26), and this group also had the highest mean dose. The excess for CML was small (RR = 1.42) and not significantly greater than 1.0. All subsequent evaluations were contfined to all leukemias excluding CLL (RR= 1.92).

Although there were large differences in the mean radiation dose received from the two treatment modalities, the risk following brachytherapy alone (RR = 1.80; mean dose = 1.7 Gy) was nearly equivalent to that following external-beam therapy (RR = 2.29; mean dose = 9.9 Gy) (Table 4). Women treated with both external-beam therapy and brachytherapy had a somewhat higher risk (RR = 2.88) than those receiving external-beam irradiation alone (RR = 1.79); however, this difference was not statistically significant (P = .13). When the excess RR was evaluated in relation to the mean weighted dose, the risk following brachytherapy alone was about 3.6 times that following external therapy.

Leukemia risks tended to be higher for patients treated with orthovoltage machines (RR = 2.80; 95% CI = 1.1-7.3), which deliver increased scatter to marrow outside the pelvic region, and for women treated with betatrons (RR = 2.87; 95% CI = 0.9-8.8); however, these differences were not statistically significant (data not shown).

Table 3. RR of leukemia associated with radiotherapy for uterine corpus cancer*

Leukemia type	Radiotherapy	Mean dose, ABM, Gy	No. of cases	No. of controls	Matched RR	95% CI
All leukemia	Yes	5.2	153	459	1.64	1.2-2.3
	No		61	290		
Non-CLL†	Yes	5.4	118	375	1.92	1.3-2.9
	No		42	247		
ANLL	Yes	5.5	90	275	2.26	1.4-3.7
	No		29	191		
CML	Yes	5.0	22	76	1.42	0.6-3.3
	No		10	48		
ALL	Yes	4.7	5	20	0.73	0.1-3.9
	No		3	8		
CLL	Yes	4.5	35	84	0.90	0.4-1.9
	No		19	43		

*Results are based on 214 case patients and 749 control subjects; four case patients and 26 control subjects were excluded due to unknown radiotherapy (non-CLL: one case patient and 19 control subjects; CLL: three case patients and seven control subjects). All RRs are adjusted for alkylating agents with the exception of the ALL group (no case patients, and one control subject exposed). ABM = active bone marrow.

†Includes one case (with four marched controls) designated myelogenous leukemia, not specified as to acute or chronic.

Table 4. RR of leukemla (non-CLL) associated with type of radiotherapy*

	Type of radiotherapy			
		External-beam therapy		
Parameter	Brachytherapy alone	Any external beam	External beam only	Plus brachytherapy
Mean dose, ABM, Gy	1.72	9.88	9.67	10.08
No. of cases	58	59	24	35
No. of controls	199	165	86	79
Matched RR	1.80	2.29	1.79	2.88
95% CI	1.1-2.8	1.4-3.7	1.0-3.2	1.6-5.1
Excess RR/Gy†	0.47	0.13	0.08	0.19
Crude RR at 1 Gy	1.47	1.13	1.08	1.19

*Results are based on 159 case patients and 611 control subjects; patients with unknown radiotherapy and with unknown type of radiotherapy are excluded. Referent group includes 42 case patients and 247 control subjects with no radiation exposure. RRs are adjusted for alkylating agents. ABM= active bone marrow.

†Excess RR/Gy = (RR - 1)/mean dose in Gy.

Dose–Response Relationship

An evaluation of leukemia risk by mean radiation dose grouped into categories is shown in Table 5. No discernible pattern in the dose–response relationship across the entire dose range could be detected, and the data appeared to be most consistent with a flat dose–response pattern or constant RR function. Significant excesses of radiogenic leukemia occurred in six of the nine dose groups. Elevations in risk of more than twofold were observed at both the low and high end of the dose scale. Analyses were recomputed including only patients with high-quality dose estimates; the results were essentially unchanged.

Fig. 1 gives the RR of non-CLL plotted against the mean marrow dose separately by radiation modality. For comparison, the RR function for leukemia mortality is presented from the Biological Effects of Ionizing Radiations (BEIR-V) model, based on data from the atomic bomb survivors *(1)*. Patients treated with brachytherapy alone were primarily given low doses that were protracted and administered at low dose rates. Here, risk appeared to increase with increasing dose to reach a peak RR of 2.6 at about 1.2 Gy and then remained significantly elevated at mean doses of 1.7 Gy. Patients receiving brachytherapy doses of 2.0 Gy or above were combined into a single group in Fig. 1 because of the small number of leukemia case patients receiving 2.5 Gy or more (n = 2). In this higher dose range, the risk appeared to level off or possibly decline. Risk estimates for the two lowest dose groups (RR = 1.5, mean dose = 0.6 Gy; RR = 2.6, mean dose = 1.2 Gy) were somewhat lower than would be predicted from the BEIR-V model, which was based on brief, whole-body, external exposures, although the results are likely to be compatible after accounting for the statistical uncertainties in the data.

Patients receiving mean radiation doses of over 5 Gy were treated with external-beam therapy, which was fractionated and given at high dose rates. Among these women, the dose–response pattern appeared to be one of increasing risk with increasing mean dose (Fig. 1). However, the confidence bounds surrounding these points are wide, and other exposure–response

Table 5. RR of leukemia (non-CLL) associated with radiation dose to the total active bone marrow, all radiation types*

Dose group, Gy	Mean dose, ABM, Gy	No. of cases	No. of controls	Matched RR	95% CI
0	0.0	42	238	1.00	R†
<1.0	0.6	9	37	1.36	0.6-3.2
1.0-1.4	1.2	12	27	2.48	1.1-5.7
1.5-1.9	1.7	18	49	2.05	1.1-3.9
2.0-2.4	2.2	17	42	2.46	1.2-4.9
2.5-4.9	3.1	3	33	0.55	0.2-1.9
5.0-7.4	6.4	5	28	1.14	0.4-3.2
7.5-9.9	8.8	19	53	1.89	1.0-3.6
10.0-12.4	10.9	15	36	2.63	1.2-5.6
≥12.5	14.9	11	21	3.03	1.2-7.4

*Results are based on 151 case patients and 564 control subjects: patients with unknown radiotherapy or with unknown radiation dose are excluded. RRs are adjusted for alkylating agents. ABM = active bone marrow.
†R denotes referent category, no radiation exposure.

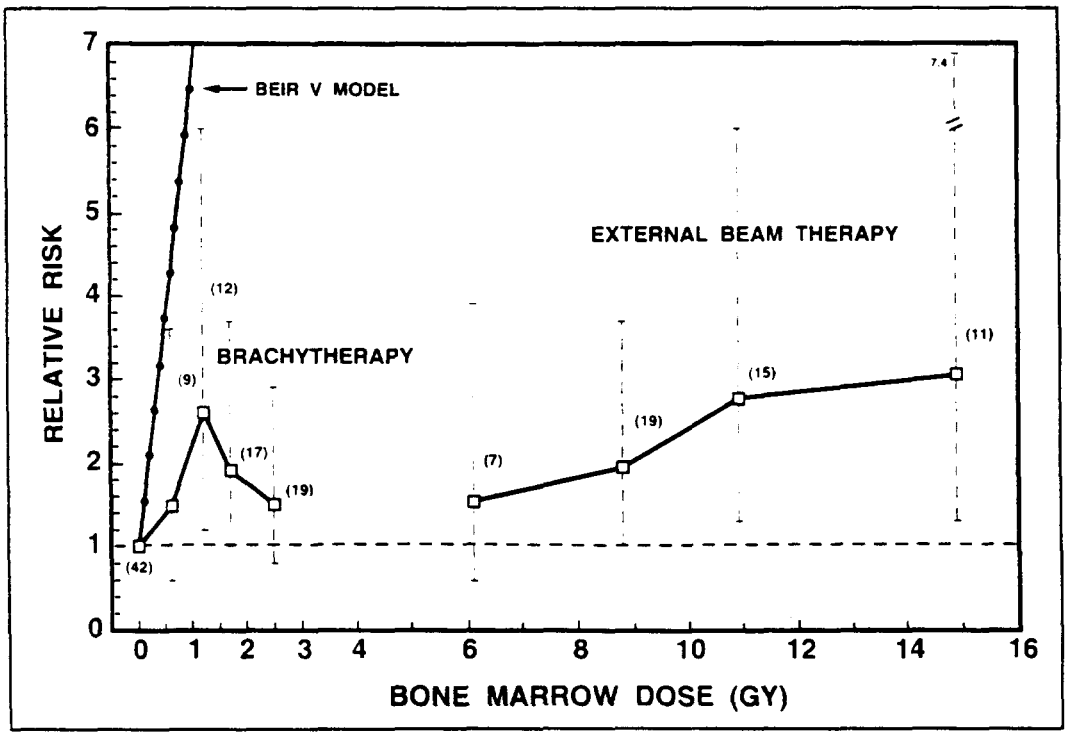

Fig. 1. Risk of leukemia (non-CLL) following uterine corpus cancer by mean weighted dose to the active bone marrow for patients treated with brachytherapy alone and for women receiving extemal-beam therapy. Patients are grouped for analysis on the basis of their mean radiation dose: brachytherapy, 0.1-0.9 Gy (mean, 0.6 Gy), 1.0-1.4 Gy (mean, 1.2 Gy), 1.5-2.0 Gy (mean, 1.7 Gy), and >=2.0 Gy (mean, 2.5 Gy); external-beam therapy, 0.1-7.4 Gy (mean, 6.1 Gy), 7.5-9.9 Gy (mean, 8.8 Gy), 10.0-12.4 Gy (mean, 10.9 Gy), and >=12.5 Gy (mean, 14.9 Gy). The number of Ieukemias in each dose group is shown in parentheses. The referent group consists of 42 case patients and 238 control subjects who were not exposed to radiotherapy (dose = 0). The 95% CIs are indicated. Also shown is the BEIR-V RR model for leukemia mortality for adults, follow-up <25 years [*(1)*. p. 168].

Table 6. Fitted dose–response excess RR models for leukemia (non-CLL)*

RR Models†	Parameter estimates (95% CI) α, per Gy	β, per Gy	Model deviance‡
All radiation types			
Null: RR = 1.0	—	—	466.15
RR = exp(βX)	—	0.69 (0.28, 1.11)	454.98
Linear (*D*)	0.10 (<0.0, 0.23)	—	457.49
Linear-exponential (*D*)	0.16 (<0.0, 0.89)	–0.02 (–0.14, 0.18)	457.45
Linear-exponential (D_i)	0.35 (<0.0, 1.38)	–0.03 (–0.12, 0.05)	456.52
Brachytherapy alone§			
Null: RR for brachytherapy = 1.0	—	—	457.95
Linear (*D*)	0.25 (<0.0, 0.77)	—	455.75
Linear-exponential (*D*)	4.69 (1.10, 13.4)	–0.90 (–1.40, –0.35)	447.75
Any external irradiation§			
Null: RR for external-beam therapy = 1.0	—	—	461.49
Linear (*D*)	0.13 (0.04, 0.27)	—	450.61
Linear-exponential (*D*)	0.05 (<0.0, 0.55)‖	0.04 (–0.26, 0.34)‖	450.52

*Results are based on 151 case patients and 564 control subjects; patients with unknown radiotherapy or with unknown radiation dose are excluded.

†Model definitions *(see* text for details): RR = exp (β *X* where *X* = 1 if radiation exposed and 0 otherwise (no relation to dose). Linear model *(D):* RR = 1 + α *D,* where *D* = mean weighted radiation dose to active marrow. Linear-exponential *(D):* RR = (1 + α *D)* (exp β *D).* Linear-exponential *(D_i):* RR = $\Sigma_i w_i(1 + \alpha D_i)$ (exp βD_i), where D_i and w_i are the radiation dose and the proportion of active marrow, respectively, for the *i* th marrow component.

‡Model deviances = –2 log-likelihood for fitted RR models. The 95% CIs are likelihood-based intervals, unless otherwise noted.

§Models evaluating a specific radiation modality also include a variable to account for other radiation types. RRs are adjusted for alkylating agents.

‖ Likelihood-based 95% Cl could not be calculated. The 95% CIs provided are based on standard errors (SE): RR ±(1.96)(SE).

relationships would be consistent with these data, including a plateau of risk in this high dose range (i.e., no relationship between risk and dose).

Several women in this study received external irradiation in which field configurations were used that resulted in substantial radiation dose to marrow in the central trunk region (sternum, thoracic spine, and ribs). Twenty-eight patients (11 case patients and 17 control subjects) had a mean dose to the bone marrow outside the pelvic region of 0.6 Gy or greater (weighted mean marrow dose after excluding doses to the lumbar spine 1-5, sacrum, pelvic bones, and upper femur). This group had a marked, significant elevation in leukemia risk (RR = 5.45; 95% CI = 2.0-15.1), and this risk differed from that based on lower doses (<0.6 Gy) to the area outside the pelvic region (RR = 1.90; 95% CI = 1.1-3.2; test of heterogeneity, *P* = .04). The majority of these patients were treated in Finland in the late

Table 7. RR of leukemia (non-CLL) associated with radiotherapy, by age and calendar year of uterine corpus cancer diagnosis, time since diagnosis, and geographic area*

Characteristic	No. exposed/total Cases	Controls	Mean dose, ABM, Gy	Matched RR	95% CI
Age at diagnosis, y					
<55	26/38	84/148	5.7	1.74	0.8-3.7
55-64	48/62	146/240	5.0	2.23	1.1-4.4
65-74	32/42	99/160	5.6	2.06	0.9-4.8
≥75	12/18	46/74	5.4	1.27	0.4-4.2
<65	74/100	230/388	5.3	2.01	1.2-3.3
≥65	44/60	145/234	5.5	1.77	0.9-3.5
Year of diagnosis					
<1960	14/21	41/81	5.9	2.00	0.7-5.5
1960-1969	27/33	84/127	4.7	2.52	0.9-6.9
1970-1979	62/86	206/335	4.8	1.66	1.0-2.9
≥1980	15/20	44/79	8.4	2.34	0.7-7.4
Time since diagnosis, y					
1-4	55/75	177/296	5.5	1.86	1.0-3.3
5-9	37/48	113/184	5.4	2.34	1.1-5.1
10-14	11/16	40/62	4.6	1.21	0.4-4.1
≥15	15/21	45/80	5.4	2.04	0.7-6.0
Geographic area					
United States	61/81	188/313	5.8	2.04	1.1-3.6
Canada	22/33	70/127	4.0	1.72	0.8-3.9
Europe	35/46	117/182	5.6	1.88	0.8-4.2

*Results are based on 160 case patients and 622 control subjects. Referent group had no radiation exposure. RRs are adjusted for alkylating agents. ABM = active bone marrow.

1950s and early 1960s, and 17 of these women were treated with an additional abdominal field, which exposed the marrow more extensively than conventional pelvic fields. This small group appeared to account for much of the upward trend in risk in the external-beam analysis; exclusion of these 28 patients (and their matched control subjects) resulted in a flattening of the dose–response function (RR = 1.8, 1.9, 1.9, and 2.0 for dose groups <7.5 Gy, 7.5-9.9 Gy, 10.0-12.4 Gy, and >=12.5 Gy, respectively).

Dose–Response Models

To further characterize the exposure-response relationship, we fit excess RR models using a continuous variable for radiation dose (Table 6). Considering all radiation types combined, there was no clear association between leukemia risk and radiation dose. A linear trend model based on the mean marrow dose, Linear *(D)*, gave no improvement in fit over a model assuming that risk depends only on radiation exposure [RR = exp (βX)] without regard to radiation dose *(D)* (P = .25). The results for the linear-exponential model *(D)* were virtually identical to that for the linear model *(D)* (P = .86); the small magnitude of the exponential "cell-killing" term (β = –0.02) indicates that there is little evidence for a downturn in risk at higher radiation doses. A model designed to better account for the anatomical heterogeneity in dose, linear-exponential (D_β), provided only a slight reduction in the deviance compared with the linear-exponential *(D)* model based on mean dose.

RR models were also fit separately by type of radiation in order to detect differences in the dose–response patterns by radiation modality. For brachytherapy, a model assuming that risk rises linearly with increasing mean dose (linear *D)* provided a poor fit to the data, and there was no significant improvement over the null model of no effect (P = .14). However, a significant linear trend was detected for doses below 1.5 Gy (excess RR = 1.05/Gy; P = .03, data not shown). Adding an exponential term to account for the observed downturn in risk at higher doses (linear-exponential *D)* gave a significantly lower deviance than the linear *D* model (P = .005), indicating a better fit. The fitted RR estimate at 1 Gy from the linear-exponential *D* model was 2.31.

Among women receiving external-beam therapy, the data were best described by a linear model based on mean dose *(D)* (P = .001; fitted RR at *1* Gy = 1.13). When analyses were restricted to irradiated women only (dose >0), the slope of the trend line was not significantly different from zero, indicating that a flat dose–response pattern is also consistent with these data.

Excess (Absolute) Risk Estimates

The excess risk of leukemia (non-CLL) associated with radiation therapy was approximated by multiplying the excess RR, i.e., RR – 1 (1.92 – 1), by the yearly incidence of all leukemias except CLL (1.556/10 000 per year) calculated from an ongoing cohort study of uterine corpus cancer patients. The number of excess leukemia cases due to radiotherapy in this population was small: about 1.4 excess leukemias per 10000 women per year at risk or only about 14 extra leukemias/10000 women over a 10-year follow-up period.

Interaction With Age, Time Since Diagnosis, and Other Factors

Muitivariate models were used to identify differences in radiogenic leukemia risk across categories of the matching factors (Table 7). No evidence was detected of variation in risk by age at diagnosis of uterine corpus cancer (test of homogeneity, P = .87). There was no indication of a higher risk occurring among women irradiated at ages under 55 years, either for all radiation types combined or by specific radiation modality. Because few studies include large numbers of elderly patients, it is noteworthy that increased risks were apparent for women older than age 65 years when irradiated (RR = 1.8) and that among these older women the elevation in risk was limited to the ANLL cell type (RR = 2.2) (data not shown). Excess leukemias related to radiation therapy were also seen in all decades of the study. Elevated risks appeared within the first 5 years after initial diagnosis, and the RR increased to 2.3 in the 5- to 9-year period. Radiogenic leukemias continued to develop 15 or more years after first treatment (RR = 2.0). Leukemias of the ANLL type accounted for all of the excess during the interval of 15+ years (14 of the 15 exposed cases, RR = 3.0). An excess of radiogenic leukemia was observed in each geographic region included in the study.

Discussion

Consistent with previous studies *(4,5,17-20)* of cancer patients treated with radiation, a modest twofold leukemia risk was evident following radiotherapy for uterine cancer. Only about 60 excess cases of leukemia occurred in this population of 110000 patients, whereas well over 1000 leukemias might have been expected if the risk estimates obtained from studies of atomic bomb survivors were applied *(21)*. This difference is likely related in part to the killing of stem cells, which occurs when high doses of radiation are absorbed by relatively small volumes of tissue.

Advantages of the current study include estimation of radiation dose by bone marrow section for each study individual, a large nonirradiated comparison group, evaluation of risk for low (<1.5 Gy) as well as high (>10 Gy) radiation exposures and low versus high dose rates, and the ability to evaluate radiation risks in an elderly population.

Leukemia risk was found to be significantly increased at about a twofold to threefold level across a wide dose range, suggesting a flat dose–response pattern. Excess leukemias occurred at about the same rate following brachytherapy as after external-beam irradiation, although the mean dose delivered by these radiation modalities differed by fivefold. These observations again indicate the important roles that cell killing, repair, and fractionation play in defining dose–response relationships.

Brachytherapy and external-beam treatments differ considerably in the manner in which radiation dose is delivered. Implanting radium or other radionuclides into the uterus for about 3 days results in a continuous exposure and much lower total dose to bone marrow than occurs from external-beam treatments (1.7 Gy versus 9.9 Gy). Also, the dose is delivered to the marrow at a much lower rate (about 0.04 cGy/min for brachytherapy versus about 10-40 cGy/min for external-beam therapy). Another dif-

ference is that external beam treatments are administered in many fractions over a period of 4-6 weeks, with each daily fraction of about 2 Gy being delivered within a few minutes. Thus, in the context of bone marrow exposure, these highly fractionated exposures at high dose rates would not be expected to be equivalent in effect to protracted exposures at low dose rates *(15,22)*.

Because of the overall fivefold difference in bone marrow dose, it is not surprising that external-beam therapy was found to be less leukemogenic, per unit dose, than brachytherapy. As dose increases, the energy deposited in cells becomes so destructive that cells are unable to divide and cellular death results. As the rate of dose delivery increases, there is also less chance for radiation damage to be repaired, increasing the risk of both cell transformation and cell killing. A recent cytogenetic study *(23)* adds support to our epidemiologic findings by demonstrating that the rate of stable chromosome aberrations per unit dose is much higher among women exposed to low-dose radium implants as compared to those exposed to high-dose external-beam therapy plus implants. Leukemia development must reflect the interplay between induction and killing of potentially transformed cells, with cell killing assuming the greater importance at high doses.

Interpretation of dose–response patterns observed in this study following partial-body irradiation is a challenge because of the multiple and competing processes involved. It is uncertain, for example, how valid the computation of bone marrow dose might be for exposures directed at one site in the body and given at different dose rates and dose fractions. In addition to nonuniform distribution of dose throughout the body, the presumed target cells for leukemogenesis, the bone marrow stem cells, are not necessarily stationary but can move through the circulatory system and repopulate depleted areas. Damaged marrow elicits a physiological response that causes stem cells to divide and migrate to injured areas.

Thus, computing dose to specific components of active bone marrow might not accurately reflect exposures to the relevant population of stem cells. The possible influence of cell killing and cell migration may be less important for brachytherapy than for external-beam treatments, however, because the cumulative marrow doses are much lower for brachytherapy and are delivered within a much shorter time interval.

Few human data are available to evaluate the risk of radiation-induced leukemia when the radiation is delivered at different dose rates or when the exposure is fractionated. Yet, such exposures are typical of environmental, medical, and occupational settings. Atomic bomb survivors received an instantaneous whole-body exposure and thus, on their own, do not provide direct information on dose rate effects. Studies of radiologists have provided limited information on this issue because of an inadequate characterization of radiation dose *(3)*. Evaluations of nuclear workers may prove useful in the future, but to date the evidence of a leukemia effect is ambiguous *(24,25)*. Comparisons of medically exposed populations irradiated for nonmalignant and malignant conditions, however, might be able to provide useful information on the leukemogenic potential of radiation delivered at different rates.

Leukemia risk following brachytherapy was examined in two previous series. Among women with benign gynecologic diseases treated with a mean dose of 0.6 Gy from intrauterine radium, 27 deaths due to acute plus nonlymphocytic leukemia were observed compared to 14.7 expected (standardized mortality rate = 1.8) *(7)*. Cervical cancer patients treated with radioactive implants alone received much higher mean doses (2.7 Gy), but they developed leukemia at a similar rate as in the benign disease cohort (RR = 2.0; 25 exposed cases) *(4)*. Our evaluation of brachytherapy was based on twice as many leukemia cases (n = 58) and found a significantly increased leukemia RR of 1.8 associated with a mean dose (1.7 Gy) that was midway between the studies on benign gynecologic disease and cervical cancer. The close agreement of results among these three studies *(4,7)* demonstrates the constancy of the approximately twofold leukemia risk associated with brachytherapy across a wide dose range.

Brachytherapy risk estimates derived from this study and previous investigations appear to be lower than would be predicted from the atomic bomb survivors. These differences could suggest that continuous low dose exposures given at low dose rates are less effective in causing leukemia or, alternatively, may reflect differences between partial-body versus whole-body exposures. Although cell killing may have reduced risk somewhat in the cancer studies, one would expect this factor to be less important for the benign gynecologic series where doses received were much lower than those for cancer patients. Several other studies of leukemia following irradiation have reported no or low risks associated with low-dose rate exposures in the low dose range, specifically studies of radioactive iodine *(26,27)*, multiple chest fluoroscopies *(28)*, diagnostic radiology *(29)*, and low dose exposures received by nuclear energy workers *(25)*. Often, however, these studies have been limited by inadequate statistical power and/or poor quantification of radiation dose.

Several investigations of cancer patients treated with high-dose external-beam therapy have reported either no *(30,31)* or only a small increased risk of subsequent leukemia *(4,5,19)*. Our findings are consistent with the twofold risk reported from the large study *(4)* of cervical cancer patients, most of whom received external-beam therapy at mean doses of 8-9 Gy. The dose–response relationship for the cervical cancer study was suggestive of a wave-like pattern, with risk declining or tapering off at the highest doses. In our study, risk appeared to rise with increasing dose, although the numbers at the highest radiation levels were small and the pattern was consistent with a flat dose–response relationship.

It is noteworthy that several women in our external beam group received meaningful radiation doses to the bone marrow in the central trunk region of the body and high doses to the pelvic marrow (most often from abdominal plus pelvic fields). This subgroup had a particularly high leukemia risk (RR = 5.5) and may have accounted for most of the upward trend in risk. Higher leukemia risks also have been observed among patients receiving radiotherapy to the spine for ankylosing spondylitis in whom substantial doses were delivered to large portions of the spine (mortality RR = 3; mean dose, 3.8 Gy) *(8,32)*. An erratic dose–response pattern was observed that was consistent with a constant relative risk across all dose groups *(32)*. In a recent

study of breast cancer *(5)* and in studies of Hodgkin's disease *(33,34)*, some patient groups treated heavily with external-beam irradiation (without chemotherapy) also were found to develop leukemia at a high rate, over fivefold.

Age at exposure in adult life does not appear to greatly influence susceptibility to radiation-induced leukemia. Similar to studies of atomic bomb survivors *(2,21)* and patients irradiated for spondylitis *(8)* and uterine bleeding *(7)*, we found that RRs were relatively constant over adult ages. However, we were able to provide risk estimates at much older ages at exposure than previous studies. A decrease in risk with age at exposure was suggested for the international cervical cancer study, but the trend was not statistically significant *(4)*. Similar to nearly all studies of radiogenic leukemia, the RR was significantly increased within the first 10 years after exposure and no increased risk was seen for CLL. We found that radiogenic leukemias of the ANLL subtypes predominated among these primarily older women, as was seen among atomic bomb survivors *(21)*, and that the increase in ANLL risk extended for more than 15 years after initial exposure. Our results showed the risk of CML to be elevated, although not as high as suggested in studies of cervical cancer or uterine bleeding *(4,7)*.

In conclusion, our study found that the leukemia risk associated with partial-body radiotherapy for endometrial cancer is small; only about 14 extra leukemias were due to radiation per 10000 women followed for 10 years. Overall, the dose–response relationship appears to be most consistent with a constant RR at all dose levels. Data from the low dose range of brachytherapy provide some evidence that continuous accumulation of dose at low dose rates may be less hazardous than that projected from the risk estimates derived from the instantaneous whole-body exposures of atomic bomb survivors. However, these conclusions must be tempered in light of the complexities and potential inaccuracies inherent in partial-body dosimetry. Further research is needed to characterize the effect on leukemia risk of fractionation and low doses when delivered at low dose rates.

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Notes

[1]Participating cancer registrles (number of case patients, number of control subjects; percent treated with radiotherapy): Connecticut Tumor Registry (33, 112; 61%); Danish Cancer Registry (33, 109; 51%): Finnish Cancer Registry (19, 66; 82%); State Health Registry of Iowa (12, 44; 62%); Los Angeles County Cancer Surveillance Program (22, 78; 54%); Michigan Cancer Foundation

(metropolitan Detroit) (14, 56; 67%); New York State Department of Health (upper New York State) (acute nonlymphotic Ieukemia case patients only: 22, 88; 64%); Cancer Registry of Norway (13, 54; 67%); Ontario Cancer Treatment and Research Foundation, Canada (50, 168: 62%).

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